Brahmwell. The specific grounds for rejection, and applicant's response thereto, are set out in detail below.

I. Rejections Under 35 U.S.C. §112, First Paragraph

All claims stand rejected under 35 U.S.C. §112, first paragraph. A number of distinct grounds for rejection are advanced. First, it is argued that the surprising result of treating p53-positive tumor cells with p53 gene therapy has not been established for tumor cells other than squamous carcinoma cells. Second, it is argued that the scope of the claims is overly broad with respect to (i) methods of gene transfer, (ii) constructs, (iii) routes of administration and (iv) combination modalities. Third, the claims are challenged in that they are not limited to delivery of wild-type p53-encoding genes. Fourth, the examiner questions the definition of the term "treatment" and whether the present invention can "cure" cancer. And fifth, it is argued that the treatment of "any and all subjects" is overly broad. Applicant traverses each of these grounds for rejection.

With respect to wild-type p53 and treatment of all subjects, the claims have been amended to clarify the invention as directed to the administration of p53 genes, encoding functional p53 molecules, to mammals. These amendments are not an acquiesence to the rejections, however. Also, the claims have been amended to remove "treatment" language, relying instead on various other terms such as inhibition of tumor growth. Again, applicant traverses the rejection and the implication that the term "treatment" must be supported by

evidence of a cure. In order to advance the prosecution, however, applicant has amended the claims in an effort to clarify the particular nature of the invention.

A. Treatment of p53-Positive Tumors

The examiner has alleged that the specification does not support treatment of "any and all cancers" given that the exemplary support is drawn to only squamous cell carcinomas. Applicant respectfully traverses for the following reasons. First, the applicability of Ad-p53 therapy to the treatment of lung cancers was first established by Zhang *et al.* (1994) and extended by the inventor for head & neck cancers (Liu I). In addition, Ad-p53 treatment of cancer now has been applied to a number of other malignancies, including breast cancer, ovarian cancer, cervical cancer, prostate cancer, nervous system cancer, colorectal cancer, liver cancer, skin cancer and bone cancer. Nielsen & Maneval (1998). Thus, the general applicability of Ad-p53 therapy to a variety of cancers has been established.

Second, there now are a number different examples showing that tumor cells carrying a wild-type p53 gene also are susceptible to p53 gene therapy. For example, Hamada *et al.*, *Gynecol. Oncol.* 60:373-379 (1996), showed that the cervical cancer-derived cell line designated as HeLa, which expresses wild-type p53, is inhibited by adenoviral p53. Hamada *et al.*, *Cancer Res.* 56:3047-3054 (1996), demonstrated a similar anti-proliferative effect with adenoviral p53 in the cervical cell lines HeLA, C4-I, MS751, ME180, CaSki and SiHa. Ko *et al.*, *Human Gene Ther.* 7:1683-1691 (1996) showed that a tumors developed from a prostate cancer line expressing wild-type p53 were inhibited by adenoviral-p53.

Further, although Harris *et al.* found a number of p53-positive cell lines that did ***not*** respond to p53 gene therapy, at least one, the neuroblastoma line SN-N-SH, did. Blagosklonny & El-Deiry, *Int. J. Cancer* 67:386-392 (1996) showed that seven cell lines (2 lung, 2 breast, 2 colon, 1 prostate) expressing wild-type p53 "underwent a dose- and time-dependent cell cycle arrest observed 20 hr after adenoviral[-p53] infection." Gomez-Manzano *et al.*, *Cancer Res.* 56:694-699 (1996), reported similar results with three, p53-positive glioma lines.

Beyond these "factual" bases for traversing the rejection, applicant submits that the rejection is defective from a legal standpoint. The examiner readily admits that "it is unclear whether [treatment of p53-postive cancers with Ad-p53] is a phenomenon unique to squamous cell carcinomas ...." It must be emphasized that it is the ***examiner's*** initial responsibility to create a *prima facie* case of non-enablement, not the applicant's to defend their presumptively enabling disclosure. *In re Marzocchi*, 169 UPSQ 370 (CCPA 1971). Merely stating that something is "unclear" cannot serve to shift this burden to the applicant.

B. Methods of Delivering Expression Constructs

While traversing the rejection in its entirety with respect to methods of delivering expression constructs, applicant has amended the claims in order to advance the prosecution. Thus, all claims now rely upon viral delivery of the expression constructs. It is beyond challenge that viral delivery is considered enabling for the transfer of genes into cells, particularly in the case of gene therapy. This is supported by numerous U.S. patents which rely upon a variety of

different viral vectors for enabling support. Applicant submits, therefore, that the issue of delivery is rendered moot by these amendments.

C. Scope of Expression Constructs

Again, applicant traverses the notion that selection of a particular type of expression construct will mean the difference between failure and success in the present invention. However, in the interest of advancing the prosecution, the claims have been amended to recite that the expression constructs all are viral expression constructs. And again, it is submitted that the skilled artisan clearly finds viral expression constructs to be sufficiently proven that the Patent Office will find such embodiments fully enabled.

D. Routes of Delivery

The examiner also indicates that direct administration of the therapeutic vector to a tumor is enabled but that other, less proven methods are not. The rejection can only impact claims 1 and 74, and claims that depend therefrom, since claims 38 and 109 (and their respective dependencies) already recite administration to a surgically revealed tumor site and catheterization of a tumor site, respectively. Regarding claims 1 and 74, these have been amended to recite "direct" administration of the vector to the tumor, thereby addressing the examiner's concerns. Again, these amendments are, in no way, an acquiescence to the rejection and are merely provided to advance the prosecution.

E. Combination Therapies

The examiner objects to claims drawn to combination therapies involving other genes, in addition to p53. The rationale behind this rejection is that the specification fails to teach which genes will be effective at augmenting the anti-tumor response of p53, and how to the deliver such genes so that they will be able to exert their effects. Applicant respectfully traverses.

As a matter of logic, this rejection cannot be sustained. The examiner is asked to reconsider the claims in light of the fact that the combination claims do not require that the second gene have "a therapeutic response" or that it synergize with p53. All that is required is that the gene be co-provided with p53. ***If the p53 administration alone is sufficient to enable a claim for inhibiting tumor growth, then dependent claims which merely add other genes must also be enabled, whether or not the other genes have any effect.*** Thus, applicant need not show that such genes are even synthesized, much less that they have an effect on the therapeutic outcome. The expression of p53 in the independent claims provides all of the necessary enablement for these claims.

II. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1, 15, 38, 74 and 109 stand rejected under 35 U.S.C. §112, second paragraph. The rejection of claims 1, 38, 74 and 109 is tied to the examiner's allegation that there is no step of the claim that relates to the preamble's recitation of treatment, and there is no indication that expression of the p53 gene product occurs in the tumor cell. Applicant has provided amendments to the claims in order to further clarify the invention and address the examiner's concerns. The rejection of claim 15 as lacking antecedent basis is addressed by cancellation of this claim.

III. Rejections Under 35 U.S.C. §102(a)

Claims 1, 3, 11, 15, 16 and 26 stand rejected under 35 U.S.C. §102(a) as anticipated by Liu I or Clayman. As evidenced by the attached declaration from Dr. Gary Clayman, the non-inventor coauthors of each of Liu I and Clayman were acting under the direction of Dr. Clayman, provided starting materials, or rendered editorial assistance to Dr. Clayman. Thus, neither Liu I or Clayman can properly be considered as "by another," and are not prior art under §102(a). Reconsideration and withdrawal of the rejection is requested.

IV. Rejections Under 35 U.S.C. §103(a)

Claims 1-20 and 26-137 stand rejected under 35 U.S.C. §103(a) as obvious over Liu I, Liu II, Clayman or Wills in view of Zhang or Brahmwell. As stated above, Liu I and Clayman are not prior art against the instant application. Thus, the primary references for this rejection are Liu II or Wills.

Liu II is said to teach growth suppression of squamous cell carcinoma of human head and neck cancer in animals following administration of adenoviral vectors encoding wild-type p53. Wills is cited for teaching the inhibition of tumor proliferation using a recombinant adenovirus expressing wild-type p53 and that repetitive administration increased survival of experimental animals and further reduced tumor growth. In addition, Wills is said to teach that p53 expression may increase tumor cell suspectibility to radiation or chemotherapy.

Zhang is said to review various cancer treatments and conclude that "combinatorial approaches using gene therapy, chemotherapy, immunotherapy and surgery is the most logical and has the greatest potential for a more advanced therapy. Brahmwell is cited for teaching various chemotherapeutic regimens and the desirability of combining them with other treatments.

Thus, the examiner posits that the benefits of p53 gene therapy were well established by the priority date for the present claims. "Therefore, given the above teachings, it would have been obvious to one of ordinary skill in the art at the time the invention was made to ... combine the methods of ... [Liu II] ... with that of Zhang *et al.* or Brahmwell to treat cancer with adenoviral vectors encoding p53 polypeptide with a reasonable expectation of success. The ordinary artisan would have been motivated to combine these references because they all discuss therapeutic models for treating cancer." Office Action at page 11.

It should be noted, however, that the only reference teaching administration of any p53 vector to p53-positive cells is Clayman, which has been removed by the attached "Katz" declaration. For claims 1-20, 26-37, 41, 74-108 and 114, this is an affirmative element of the claims and cannot be ignored. A careful review of the remaining references will illustrate that this concept was neither suggested nor contemplated prior to applicant's invention.

For example, the examiner cites from the Wills reference: "By resuppplying functional p53 to these tumors, it is possible that they will now become susceptible to apoptosis ...." The idea here is that ***replacement*** of missing p53 functions will restore normal growth control to tumor cells. In addition, both Wills and Liu II note that mutation of the p53 gene is the most common genetic defect in human cancers, and indicate that ***correction*** of this defect is a viable therapeutic option. Clearly, these references take, as their departure point, the need to ***restore*** p53 function to cells that have somehow lost this important anti-tumor activity. Missing from this discussion, either explicitly or implicitly, is the notion that cells which already ***have*** functional p53 may nonetheless benefit from provision of an exogenous p53 polypeptide via gene therapy.

Thus, it is respectfully submitted that those of skill in the art would not have considered p53 ***supplemental*** therapy an obvious extension of p53 ***replacement*** therapy. The two concepts are completely distinct and, in the absence of some indication that one would have thought this a useful undertaking, a *prima facie* case will not stand. Thus, at least for claims 1- and 74- , the

references fail to teach or suggest an element of the claims and, therefore, the rejection is improper.

Turning to the remaining independent claims, applicant notes that the examiner has not cited any references that teach either treatment of microscopic residual disease (claim 38) or continuous perfusion (claim 109) and, thus, on its face the rejection is improper. Further, it should be noted that these endeavors cannot be dealt with simply as obvious extensions of the basic treatment regimen discussed, for example, in Liu II. That this is the case can be deduced by reference to the examiner's own discussion of the enablement issue, where numerous concerns are set forth that would give the hypothetical skilled artisan reason to, at the very least, question such distinct clinical methods.

V. Summary

In light of the foregoing amendments and remarks, applicant submits that all claims are in condition for allowance and solict an early indication to this effect. Should Examiner Hauda have any questions regarding this response, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Steven L. Highlander
Reg. No. 37,642

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Arnold, White & Durkee
P.O. Box 4433
Houston, TX
512-418-3000